In the Specification

Please replace the paragraph at page 2, lines 4 through 21 with the following paragraph:

As described herein, the ARSACS gene, referred to herein as "*spastin*" (also known as *sacsin*), has been mapped to chromosome 13q11 by linkage analysis and cloned from human, mouse and hamster. The gene was identified by using fine-structure linkage disequilibrium (LD) mapping to narrow the disease interval and then performing sample-sequencing to identify candidate genes. The *spastin* gene has a remarkable feature in that it contains a large exon spanning at least 12,793 base pairs of genomic DNA and comprises an open-reading frame of 11,487 base pairs. As described herein the gene is highly conserved in mouse. This exon of *spastin* is the largest found in any vertebrate organism. The deduced protein contains three large domains with sequence similarity to each other, as well as to the protein predicted to be encoded by an open reading frame identified in *Arabidopsis* genomic DNA. These domains contain a subdomain with sequence similarity to heat-shock proteins, suggesting a role in chaperone-mediated protein folding. *Spastin* appears to be expressed in a wide variety of tissues including brain and central nervous system. Alterations in the *spastin* gene have been identified as described herein which correlate strongly with ARSACS, including at least two alterations which have severe effects on the encoded protein, providing strong evidence that mutations in the open reading frame of the *spastin* gene are responsible for ARSACS.

Please replace the paragraph at page 9, lines 13 through 25 with the following paragraph:

A 20 kb sequence contig revealed a huge genomic open reading frame (ORF) of 11,487 base pairs that encodes 3829 amino acids (SEQ ID NO: 2). The open reading frame (ORF) begins with an AUG codon preceded by an in-frame stop codon 75 bp upstream and continues for a total of 3,829 codons before encountering a stop codon. One large cDNA (KIAA0730) derived from a brain library and over 30 ESTs overlap the ORF and allowed the determination of the 3' untranslated region (UTR), which extends 1,307 bp to a polyadenylation site (Figure 1). The existence of this gigantic exon was confirmed by analyzing RT-PCR products spanning the

entire mRNA; this analysis showed perfect correspondence between the mRNA and genomic DNA sequence. Thus, the total length of the exon must be at least 12,793 bp. A probe derived from within this sequence detects a transcript of approximately 12.8 kb on a Northern blot, suggesting that the identified exonic sequence may constitute an intronless gene, although the possibility of a small 5' exon cannot be excluded.

Please replace the paragraph at page 13, ~~lines 8 through 19 with the following~~ paragraph:

As described herein, sample-sequencing of the ARSACS critical region, in combination with directed sequencing of specific subclones and computer-aided analysis led to the characterization of a very large exon directly from genomic DNA. This likely represents the entire coding sequence of the *spastin* gene as the first methionine is preceded by an in-frame stop codon 75 bp upstream. RT-PCR demonstrated that the sequence, from this 75 bp until the polyadenylation site, is transcribed. *Spastin* appears to be an intronless gene, although a non-coding upstream exon cannot be ruled out. The *spastin* exon of at least 12,793 bp encoding an ORF of 11,487 bp represents the largest exon and the largest ORF within an exon found in any vertebrate so far. The next largest exons reported are the X (inactive)-specific transcript (*XIST*) (11,363 bp) which does not code for a protein (13), and the large central exon of the mucin gene (*MUC5B*) which is 10,713 bp long (14).

Please replace the paragraph at page 42, lines 22 through 28 with the following paragraph:

~~Computational Analyses~~

~~World Wide Web-based hyper -text (http) sequence analysis included (using default~~ parameters):

BLAST: ncbi.nlm.nih.gov/cgi-bin/BLAST/nph-nesblast?Jform=1;

FASTA: ebi.acc.uk/searches/fasta.html;

PSORT: psort.nibb.acc.jp:8800;

~~EXPASY Proteomics tools: expasy.ch/tools/;~~